Docket No. 455-023 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

JEFFREY S. KIEL, ET AL.

Serial No.: 10/806,260 Group Art Unit: 1621

Filed: 03/22/2004 Valenrod, Yevgeny

For: **PHENOLIC ACID SALTS OF GABAPENTIN IN LIQUID AND/OR SEMI-SOLID DOSAGE FORMS AND METHODS OF USE**

DECLARATION OF RICHARD ANDREW TODEBUSH, PH.D.

I, Richard Andrew Todebush, Ph.D., hereby declare as follows:

1. I received a Bachelor of Science (B.S.) degree in Chemistry from Western Carolina University in 1996 and a Doctor of Philosophy (Ph.D.) in Analytical Chemistry from the University of Georgia in 2001.
2. I worked as a research chemist for Unilever, Chicago, Illinois, in the development of personal care products from 2001 to 2004. In 2004, I started working for Kiel Laboratories, Inc. (Kiel) as a Senior Research Scientist and in 2006 I became the Research and Development Manager.
3. I currently manage the Research and Development Department for Kiel Laboratories, Inc. My responsibilities include investigating new active

pharmaceutical ingredients for use in Kiel's manufacturing processes, which include the preparation of tannic acid containing compositions.

4. I have read the specification and claims of the above-referenced patent application, as well as the Office Action mailed August 27, 2007, in the present application and the prior art references cited by the Examiner.

When Drs. Jeffrey Kiel, Greg Thomas, and Narashimhan Mani made their invention of the formation of gabapentin tannate, to the best of my knowledge, there were no publications or information available that suggested it was possible to prepare a tannate salt of gabapentin.

6. Before, the invention of Dr. Kiel, et al., it was generally expected that the close proximity of the carboxylic acid group to the positively charged amine functional group on the gabapentin molecule would prevent the formation of the tannate salt. I was surprised that the inventors of the present application were able to prepare a gabapentin tannate salt.

I have reviewed U.S. Patent No. 6,383,471 ('471) to *Chen et al.* As stated in the title and throughout the Specification, it was clear to me that the '471 patent applied only to ionizable hydrophobic therapeutic agents having intrinsic water solubilities of less than 0.1% or 0.01% by weight.

8. Not knowing whether gabapentin was water-soluble, or water-insoluble, I would have checked the Merck Index or, perhaps, the Handbook of Chemistry and Physics.

9. The Merck Index has been the accepted gold standard reference for the pharmaceutical arts since 1889. Gabapentin is listed in the Merck Index as having a solubility in water at pH 7.4 which exceeds 10% (see Appendix 1). I was surprised to see gabapentin listed as one of the hydrophobic therapeutic agents in the '471 patent in col. 6, line 33; col. 7, line 2; col. 8, line 21; col. 9, line 23; col. 44, line 42; col. 45, line 12; col. 46, line 62; and col. 47, line 64. It was interesting to note that gabapentin was never included as one of the more or most preferred hydrophobic therapeutic agents.

10. In my opinion, gabapentin was mistakenly listed as a hydrophobic therapeutic agent in the '471 patent and one of ordinary skill in the art, like myself, would either have

recognized that mistake or checked the solubility in a standard reference generally used by the pharmaceutical industry such as the Merck Index.

11. It is also my opinion, that I would not have relied on the '471 patent to guide me in an attempt to prepare a gabapentin tannate salt because the '471 patent deals exclusively with hydrophobic therapeutic agents of which gabapentin is not one. I would not have noticed that gabapentin was even listed as 1 of the 300+ therapeutic agents because they were all identified as being hydrophobic. Additionally, tannic acid is identified as only 1 of 32 pharmaceutically acceptable acids. I found no suggestion in the '471 patent that tannic acid could be combined with gabapentin.

12. I have reviewed U.S. Pat. No. 6,287, 597 ('597) to *Gordziel* and I have read the Examiner's comments in the Non-final Rejection mailed August 27, 2007. The Examiner appears to be confusing the use of excipients, such magnesium aluminum silicate (MAS) in preparing suspensions, as disclosed in *Gordziel*, that already have certain tannate salts already present, with that of the invention of the present application which uses MAS to prepare the actual tannate salt of gabapentin.

13. In my opinion, if I were faced with the challenge of preparing a tannate salt of gabapentin, I would not have a reasonable expectation that a gabapentin salt could have been successfully made based on either the '471 or the '597 patent.

I declare further that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made under penalty of perjury with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 11-27-07

By: R. Andrew Todebush

Richard Andrew Todebush, Ph.D.

APPENDIX I

THE
MERCK INDEX

AN ENCYCLOPEDIA OF
CHEMICALS, DRUGS, AND BIOLOGICALS

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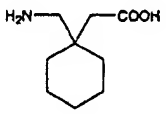
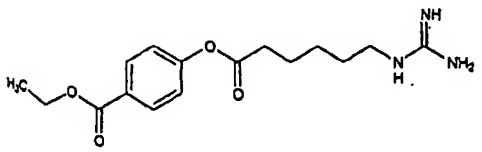
4343. Gabapentin. [60142-96-3] 1-(Aminomethyl)-cyclohexaneacetic acid, CI-945; GP-3450; GOE-3450; Neurontin. $C_9H_{17}NO_2$, mol wt 171.24. C 63.13%, H 10.01%, N 8.18%, O 18.69%. Amino acid structurally related to γ-aminobutyric acid (GABA), q.v., designed to cross the blood brain barrier. Prepn: G. Satzinger *et al.*, DE 2460891 (1976 to Gödecke); *eidem*, US 4024175 (1977 to Warner-Lambert). Pharmacokinetics and metabolism: K.-O. Vollmer *et al.*, *Arzneimittelforsch.* 36, 830 (1986). Clinical pharmacology: B. Saletu *et al.*, *Int. J. Clin. Pharmacol. Ther. Toxicol.* 24, 362 (1986). GC determn in biological fluids: W. D. Hooper *et al.*, *J. Chromatog.* 527, 167 (1990). Review of pharmacology and clinical trials in epilepsy: B. Schmidt in *Antiepileptic Drugs*, R. H. Levy *et al.*, Eds. (Raven Press, New York, 3rd ed., 1989) pp 925-935; K. L. Goa, E. M. Sorkin, *Drugs* 46, 409-427 (1993). Clinical trial for treatment of pain in diabetic neuropathy: M. Backonja *et al.*, *J. Am. Med. Assoc.* 280, 1831 (1998). Clinical evaluation in social phobia: A. C. Pande *et al.*, *J. Clin. Psychopharmacol.* 19, 341 (1999).



Crystals, mp 165-166° (Satzinger); also reported at mp 172-173° (Schmidt). pK_{a_1} (25°) 3.68; pK_{a_2} 10.70. Isoelectric point 7.14. Solubility in water at pH 7.4 exceeds 10%.

THERAP CAT: Anticonvulsant.

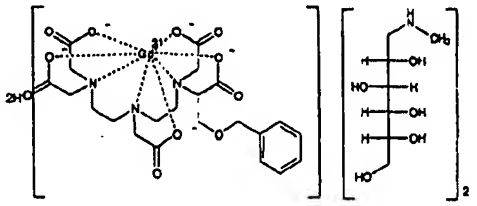
4343. Gabexate. [59892-01-8] 4-[[6-[(Aminoiminomethyl)amino]-1-oxohexyl]oxy]benzoic acid ethyl ester; *p*-hydroxybenzoic acid ethyl ester 6-guanidinohexanoate; *p*-carbethoxyphenyl ε-guanidinocaproate. $C_{16}H_{23}N_3O_4$; mol wt 321.37. C 59.80%, H 7.21%, N 13.08%, O 19.91%. Non-peptide proteolytic enzyme inhibitor which also inhibits the hydrolytic effects of thrombin, plasmin, and kallikrein, trypsin but not chymotrypsin; *cf.* aprotinin. Prepn as the *p*-toluenesulfonate salt: S. Fujii, T. Watanabe, DE 2050484; *eidem*, US 3751447 (1971, 1973 both to Ono). Enzyme inhibition: M. Muramatu, S. Fujii, *Biochim. Biophys. Acta* 268, 221 (1972); S. Tamura *et al.*, *Ibid.* 484, 417 (1977). Pharmacology: T. Okegada *et al.*, *Nippon Yakurigaku Zasshi* 71, 71 (1975), *C.A.* 84, 218m (1976). Metabolism: M. Sugiyama *et al.*, *Oyo Yakuri* 9, 733 (1975), *C.A.* 83, 188145e (1975). Metabolism of inhibitory effect on platelet aggregation: G. Kosaki *et al.*, *Thromb. Res.* 20, 587 (1980). Beneficial action in traumatic shock: A. M. Lefer *et al.*, *IRCS Med. Sci. Libr. Compend.* 8, 278 (1980); in exptl acute pancreatitis: J. S. Wiener *et al.*, *Pancreas* 2, 181 (1987). Comparative clinical study in acute pancreatitis: N. Tanaka *et al.*, *Adv. Exp. Med. Biol.* 120, 367 (1979). Teratology and toxicity study: S. Fujita *et al.*, *Oyo Yakuri* 9, 743 (1975), *C.A.* 83, 188322x (1975).



Methanesulfonate. [56974-61-9] Gabexate mesylate; FOY; Megacen. $C_{16}H_{23}N_3O_4.CH_3SO_3H$; mol wt 417.48. White crystals. Sol in water, ethanol, chloroform. Slightly sol in acetone. Practically insol in ether. pH of soln (1:100): 4.0-5.0. LD_{50} in mice (mg/kg): 8000 orally; 4700 s.c.; 25 i.v. (Fujita).

THERAP CAT: Enzyme inhibitor (proteinase).

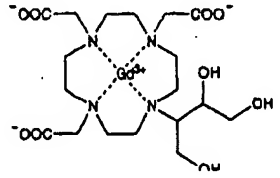
4344. Gadobenate Dimeglumine. [127000-20-8] 1-Deoxy-1-(methylamino)-D-glucitol [4-(carboxy-κ*O*)-5,8,11-tris[(carboxy-κ*O*)methyl]-1-phenyl-2-oxa-5,8,11-triazatridecan-13-oato(5−)-κN^5,κN^8,κN^{11},κO^{13}]gadolinate(2−) (2:1), gadolinium benzyloxypropionictetraacetate dimeglumine; Gd-BOPTA/Dimeg; B-19036/7; MultiHance. $C_{36}H_{62}GdN_5O_{21}$; mol wt 1058.28. C 40.85%, H 5.92%, Gd 14.86%, N 6.62%, O 31.75%. $C_{22}H_{26}GdN_3O_{11}.2C_7H_{17}NO_5.2H$. Intravascular paramagnetic MRI contrast agent. Prepn: E. Felder *et al.*, EP 230893; *eidem*, US 4916246 (1987, 1990 both to Bracco); F. Ungerti *et al.*, *Inorg. Chem.* 34, 633 (1995). HPLC determn in biological samples: T. Arbughi *et al.*, *J. Chromatog. B* 713, 415 (1998). Physicochemical properties: C. de Haen *et al.*, *J. Computer Assist. Tomog.* 23, Suppl. 1, S161 (1999). Pharmacology: P. Tirone *et al.*, *ibid.* S195. Pharmacokinetics: V. Lorusso *et al.*, *ibid.* S181. Toxicology: A. Morisetti *et al.*, *ibid.* S207. Clinical study in MRI of liver lesions: J. Petersein *et al.*, *Radiology* 215, 727 (2000). Review of clinical studies: B. Hamm *et al.*, *J. Computer Assist. Tomog.* 23, Suppl. 1, S53-S60 (1999).



Hygroscopic powder. mp 124°. Freely sol in water, sol in methanol. Practically insol in *n*-butanol, *n*-octanol, chloroform. Abs max 257.8 nm (ε 203). $[\alpha]_{365}^{20}$ −26.9° (*c* = 1.45 in water). Prepd as 0.5*M* soln, osmolality (37°) 1.97 mol/kg. d^{20} 1.22. Viscosity (mPa.s): 9.2 (20°), 5.3 (37°). LD_{50} i.v. in mice (mmol/kg): 5.7 (at 1 mL/min), 7.9 (at 0.2 mL/min); LD_{50} i.v. in rats (mmol/kg): 6.6 (at 6 mL/min), 9.2 (at 1 mL/min) (Morisetti).

THERAP CAT: Diagnostic aid (MRI contrast agent).

4345. Gadobutrol. [138071-82-6] [10-[2,3-Dihydroxy-1-(hydroxymethyl)propyl]-1,4,7,10-tetraazacyclododecane-1,4,7-triacetato(3−)-N^1,N^4,N^7,N^{10},O^1,O^4,O^7]gadolinium; Gd-DO3A-butrol; Gadovist. $C_{18}H_{31}GdN_4O_9$; mol wt 604.78. C 35.75%, H 5.18%, Gd 26.00%, N 9.27%, O 23.81%. Neutral, macrocyclic gadolinium chelate. Prepn: J. Platzek *et al.*, EP 448191 (1991 to Schering AG). Physicochemical properties and *in vivo* imaging studies: H. Vogler *et al.*, *Eur. J. Radiol.* 21, 1 (1995). Clinical pharmacokinetics: T. Sinks *et al.*, *Invest. Radiol.* 29, 709 (1994). Clinical evaluation of diagnostic use for cerebral metastases: T. J. Vogl *et al.*, *Radiologe* 35, 508 (1995); for glioblastomas: M. Hartmann *et al.*, *Fortschr. Röntgenstr.* 164, 119 (1996).



Hydrophilic. Osmolality (osmol/kg): 0.57 (0.5 mol/l); 1.39 (1 mol/l). Viscosity (cP): 1.43 (0.5 mol/l); 3.7 (1 mol/l). Partition coefficient (butanol/water): 0.006. LD_{50} i.v. in mice: 23 mmol/kg (Vogler).

THERAP CAT: Diagnostic aid (MRI contrast agent).

4346. Gadodiamide. [131410-48-5] [5,8-Bis(carboxymethyl)-11-[2-(methylamino)-2-oxoethyl]-3-oxo-2,5,8,11-tetraazatridecan-13-osto(3−)]gadolinium; gadolinium diethylene-